20. (Amended) The cell of claim 19, said alpha subunit being encoded by a first expression vector and said beta subunit being encoded by a second expression vector, said first and said second vectors each comprising at least the 69% transforming region of the bovine papilloma virus genome.

Add new claims 45 and 46.

--45. (New) The cell of claim 5, said cell being a mammalian cell.--

--46. (New) A cDNA sequence encoding the beta subunit of human LH.--

REMARKS

Applicants wish to express their appreciation for the telephonic interview granted the undersigned and Scott Chappel on July 14, 1987. During that interview, the rejection of the claims under 35 U.S.C. §112, for overbreadth, and 35 U.S.C. §103, for obviousness, were discussed. Before recapitulating that interview, we address the more technical rejections under §112, which were not discussed during the interview.

On page 3 of the Office Action it is requested that the correspondence of ATCC numbers and deposited cells be clarified. Cells (C127) transformed with the vector pRF 398 alpha t_2 are, as stated in the preliminary amendment filed on July 24, 1984, given ATCC No. CRL 8400. The ATCC No. CRL 8401 is given to C127 cells transformed with pRF 375 and to C127

cells transformed with pRF 398; as is stated in the preliminary amendment, the latter two cells have the same number because a mixture of the two cells was deposited.

The objection to the deposit-related declaration is met by the enclosed declaration of availability, which satisfies the requirements of MPEP §608.01(p)(C).

The rejection of the claims under 35 U.S.C. §112, second paragraph, for indefiniteness, has been met by the present amendment.

Regarding the provisional obviousness-type double patenting rejection of the claims, upon allowance, the appropriate terminal disclaimer will be filed.

Before summarizing the references and the nonobviousness arguments discussed during the interview, we direct the Examiner's attention to new claim 46, directed to a cDNA encoding the beta subunit of human LH. As was emphasized during the interview, applicants were the first to obtain this cDNA, despite the long period of time during which the alpha subunit had already been cloned (see the earlier Fiddes et al. paper). As was explained by Dr. Chappel during the interview, there is good reason for the long period of time separating the cloning of the alpha and beta subunits. As is well known, the alpha subunit is common to LH, FSH, and hCG. The alpha subunit was thus a fairly routine cloning task, given the fact that hCG is plentiful in placental tissue, which is available in large

amounts, and which contains very high concentrations of high quality mRNA encoding hCG, from which both the alpha and beta subunits were readily cloned by Fiddes et al. The beta subunit of LH is a different matter; the mRNA for it is not found in placental tissue, and must be obtained from pituitary tissue which, as Dr. Chappel explained, is much less readily available, and contains a much lower concentration of useable, non-degraded mRNA. It is submitted that this long period of time between the cloning of the hCG subunits and applicants' cloning of the beta subunit of LH, coupled with the inherently far greater difficulty of achieving the latter, supports the patentability of new claim 46.

We turn now to the prior art rejections discussed during the interview. The primary references are the two Fiddes et al. papers; Pierce et al.; Moriarty et al.; and Rice et al.

At the outset it was pointed out, and is reiterated here, that none of the references of record even suggested, let alone achieved, applicants' invention, the production of a human fertility hormone in one cell transformed with DNA encoding both the alpha and beta subunits, which are processed and assembled into a biologically functional dimeric hormone within that cell. This is so despite the fact that there has long been a need for a means of making pure hormones which can be used in controlled proportions to induce ovulation in

infertile women (see the discussion of the Frustaci septuplets in a previous response). One can only assume that applicants' pioneering work was not attempted, nor even suggested, by others in the field either because no one thought of the idea, or other workers assumed it would not work. Witness the two Fiddes papers, which show that, by 1981, cDNA's encoding both the alpha and beta subunits of hCG existed, and presumably could have been transformed into a eukaryotic cell as applicants later did had anyone thought of doing so, yet this was not done, despite the above-mentioned need.

During the interview, the relationship between the previously-submitted Pierce declaration, which counters the rejection over the Pierce et al. paper, and the Moriarty et al. publication was discussed. As the Pierce declaration pointed out, the Pierce et al. paper described in vitro association work in which a naturally occurring dimeric hormone, which had already been synthesized and properly folded and processed, was treated to cause disassociation and then allowed to reassociate, not within living cells, but in a test tube. This deficiency of the Pierce et al. paper is in no way made up for by the teaching of Moriarty et al., simply to the effect that a recombinant mammalian cell is capable of glycosylating a protein encoded by a cDNA. Moriarty deals only with a monomeric protein, and teaches nothing whatsoever about the ability of two different, separately-encoded protein chains to associate in a cell to form a biologically functional dimer.

Nor does Rice et al. make up for the deficiency for the Pierce et al. paper. Rice et al., unlike the invention, involves a recombinant cell in which one of the two chains of a dimer (the heavy chain of an antibody) is already being produced by the cell prior to transformation with DNA encoding the light chain. That functional antibody was produced by such cells in no way predictive that a cell in which both chains are encoded by recombinant DNA molecules will produce a dimer in which the chains properly associate, and which is biologically functional. In addition, the Examiner's statement, on page 8 of the Office Action, that "Rice et al. also support the fact that mammalian cells are capable of assembling complex proteins in cells which do not normally produce these proteins", is incorrect; the lymphoid cells of Rice et al. are, in fact, cells normally capable of producing functional dimeric antibody, which have been transformed virally so as to lose the ability to make heavy, but not light, antibody chain. There is simply nothing in Rice et al. to suggest making a dimer using two recombinant DNA molecules.

The other issue discussed during the interview was whether the claims should be limited to mammalian cells, as suggested by the Examiner, or whether their current breadth, encompassing any eukaryotic cell, is justified. It is submitted that, given the pioneering nature of applicants' invention, the current scope is proper, and, indeed, it would

be unfair to limit the claims as suggested and thus allow an infringer to take advantage of applicants' discovery, in the context of a new eukaryotic cell type, for example, insect cells, which were not even in use at the time the invention was made. It is submitted that, once applicants gave the world the knowledge that these dimers can properly be assembled in recombinant cells, the possibility was then opened up of using a wide variety of cell types, all of which could not possibly be tested by one group of workers, and these should be encompassed by the claims.

Finally, there was a brief discussion of the Hsiung declaration, submitted previously to swear behind Ochi et al. paper. The Examiner questioned whether the cells mentioned in the notebook page actually produced biologically active dimeric hCG. The undersigned explained that Dr. Hsiung had told him that the cells, in fact, had produced such dimeric hCG, but the assays proving this had not been carried out at the time the notebook page written, but were carried out at a later time. The declaration was signed only by Dr. Hsiung because it was she who carried out the experiment, without the assistance of the other inventors.

In view of the above, it is submitted that all of the claims in the application are in condition for allowance, and such action is requested.

Respectfully submitted,

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